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"RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE EXAMINING
GROUP 1615"

#23
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AUG 28 2003
PATENT & TRADEMARK OFFICE

DOCKET NO: 0010-1106-0

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
HITOO NISHINO ET AL	: EXAMINER: KISHORE, G.
SERIAL NO: 09/556,701	:
FILED: APRIL 24, 2000	: GROUP ART UNIT: 1615
FOR: PHARMACEUTICAL OR FOOD COMPOSITION FOR TREATMENT OR PREVENTION OF BRAIN EDEMA	:

DECLARATION UNDER 37 C.F.R. § 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

Now comes Dr. Kunio Torii, who deposes and states that:

(1) A copy of my *Curriculum Vitae* is attached.

(2) I am an inventor in the above-identified application.

(3) I have been informed that the U.S. filing date of the above-identified application is April 24, 2000.

(4) I have read and am familiar with the specification and pending claims of the above-identified application.

(5) I have read and am familiar with the contents of the Official Action dated December 2, 2002 in the above-identified application.

(6) I have also read and familiar with the following references discussed in the Official Action dated December 2, 2002 in the above-identified application:

(a) WO 97/205,555 (hereinafter referred to as "WO '555"),

(b) U.S. 5,137,871 (hereinafter referred to as "U.S. '871"),

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(c) U.S. 5,520,912 (hereinafter referred to as "U.S. '912"), and

(d) U.S. 4,687,763 (hereinafter referred to as "U.S. '763").

(7) The field of the present invention is the pharmaceutical treatment of brain disorders.

(8) I consider myself to be an expert in the field of the invention described above. I base this opinion on the facts that I have worked in the field of the invention for more than 30 years and published many scientific articles as described in my *Curriculum Vitae* attached hereto.

(9) I have carefully read WO '555. I find no description in that reference of treating brain edema with melatonin.

(10) WO '555 describes a method for treating or preventing anoxic or ischemic brain injury by administering melatonin. See the Abstract.

(11) WO '555 does not mention brain edema at all.

(12) Brain edema is a condition in which excess fluid accumulates in brain tissue, which results in the swelling of the brain tissue. That this is so is demonstrated by the specification of the above-identified application at page 1, lines 14-16 and U.S. '871 at column 3, lines 39-43.

(13) Nowhere is it stated in WO '555 that the subjects described therein were suffering from the symptoms of brain edema described above.

(14) It is true that ischemia is a cause of brain edema. However, the fact that a subject has an ischemic brain injury does not mean that the subject must also have brain edema. Thus, it is possible that a subject has an ischemic brain injury but does not have brain edema.

(15) In fact, there is no direct relationship between the clinical symptoms of ischemic patients and brain edema. This makes the clinical effect of melatonin on the brain uncertain.

(16) The Examiner in charge of the above-identified application appears to agree with the statement made in paragraph (14) above. At page 3, lines 6-9 of the Official Action dated December 2, 2002, the Examiner stated:

> Applicants argues that the subject has an ischemic brain injury does not mean that the subject has brain edema. ***This might be true***; however, if a person has ischemia caused by brain edema, then by treating the ischemia, one is treating the edema also and instant claims do not exclude the condition. [Emphasis added.]

(17) However, there is nothing in WO '555 which suggests that the subjects treated with melatonin as described therein were suffering from brain edema. Therefore, the Examiner is only speculating that the subjects described in WO '555 were also suffering from brain edema, in addition to ischemia. There is no evidence in WO '055 which supports the Examiner's speculation, since there is no mention at all of brain edema in that publication. Thus, the Examiner has failed to establish that the subjects described in WO '555 were necessarily suffering from brain edema.

(18) In addition, as shown at page 21 of WO '555, the mild 4-vessel occlusion model (which is also referred to as 4VO, 10 minute occlusion) was used to demonstrate the therapeutic efficacy in treating brain ischemia with melatonin.

(19) The 4VO model is not used by workers in the field of the invention to measure the therapeutic effect of an agent for treating brain edema. This is because the 4VO model is well known in the field of the invention to suffer from a variety of problems relating to the identification of agents which are useful for treating brain edema.

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(20) In my opinion, the disclosure of WO '555 would not have suggested a method of treating brain edema by administering melatonin to a subject having brain edema to one of ordinary skill in the field of the field of the invention at the time the above-identified application was filed in the U.S. My opinion is based on the facts that (a) a subject having an ischemic brain injury does not necessarily also have brain edema, (b) there is no direct relationship between the clinical symptoms of ischemic patients and brain edema which makes the clinical effect of melatonin on the brain uncertain. Thus, in my opinion, one of ordinary skill in the field of the field of the invention at the time the above-identified application was filed in the U.S could not have predicted with a reasonable expectation of success that melatonin could be used to treat brain edema based on the disclosure of WO '555.

(21) U.S. '871 describes a treatment to reduce edema for brain and musculature injuries. See the Abstract.

(22) U.S. '871 at column 3, lines 39-51 states:

> Brain edema refers to a condition in which there is increased water content in brain tissue. This condition occurs when there is a breakdown in the function of blood vessels that normally separate blood constituents from brain tissue. Brain blood vessels become more permeable when they are injured by a lack of oxygen, by toxic substances generated in injured tissues, or by unknown causes such as those associated with brain hemorrhage of the newborn. The medical conditions associated with brain edema are: brain ischemia, brain infarction, brain tumors, brain infarctions and abscesses, brain trauma and contusions, and secondary brain damage arising from neurosurgical operations.

(23) Thus, a subject suffering from brain edema may also be suffering from brain ischemia.

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(24) However, as noted above, the fact that that a subject is suffering from brain ischemia does not necessarily mean that the subject is also suffering from brain edema. In other words, a subject may suffer from brain ischemia but not suffer from brain edema.

(25) Again, as noted above, there is no direct relationship between the clinical symptoms of ischemic patients and brain edema. This makes the clinical effect of melatonin on the brain uncertain.

(26) U.S. '912 describes the prevention and treatment of ischemic events and reperfusion injury resulting therefrom using Lys-plasminogen. See the Abstract.

(27) At column 3, line 6 to column 4, line 6, U.S. '912 states that brain ischemia can cause brain edema.

(28) However, as discussed above, a subject suffering from brain ischemia does not necessarily also suffer from brain edema, i.e., a subject may suffer from brain ischemia but not suffer from brain edema.

(29) U.S. '763 describes a composition and method for increasing levels or release of brain serotonin. The composition contains melatonin. See the Abstract.

(30) U.S. '763 fails to describe or suggest administering melatonin to treat brain edema, since that patent fails to mention brain edema at all.

(31) In view of the foregoing, U.S. '872, U.S. '912, and U.S. '763 fail to remedy the deficiencies of WO '555. Accordingly, it is my opinion that WO '555 taken in any combination with those patents fails to suggest a method of treating brain edema by administering melatonin to a subject having brain edema to one of ordinary skill in the field of the field of the invention at the time the above-identified application was filed in the U.S.

(32) I declare further that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

(33) Further Declarant saith not.

Kunio Torii (signature)
Kunio Torii

Aug. 26, 2003
Date

Last Updated: May 7, 2003

Kunio Torii

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Personal Date of Birth: September 25, 1946 Birthplace: Tokyo, Japan Sex: Male

Award

1985 Encouragement Award of Japanese Society of Nutrition and Food Science

Educational Degrees

1971 Bachelor of Science, Department of Veterinary Medicine, Faculty of Agriculture, University of Tokyo, Tokyo, Japan

1976 D.V.M., Department of Veterinary Medicine, Faculty of Agriculture, University of Tokyo, Tokyo, Japan

1986 PhD, Department of Agriculture and Chemistry (Animal Nutrition), Faculty of Agriculture, University of Tokyo, Tokyo, Japan

Professional Experiences

1971-1995 Assistant Department Manager
Science Laboratories, Central Research Laboratories, Ajinomoto Co., Inc., Kawasaki, Japan

1977-1979 Visiting Scientist
Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, PA, USA

1990-1995 Director of Torii Nutrient-Stasis Project
Exploratory Research for Advanced Technology, Research Development Corporation of Japan (renamed to Japan Science and Technology Corporation since 1996)

1995-2001 Senior Researcher
Basic Research Laboratories, Central Research Laboratories, Ajinomoto Co., Inc., Kawasaki, Japan

1996-1999 Partnership (liaison) of the national project on Neuronal Stem Cell Transplantation into the Lesioned Area of the Brain (i.e. for Perkinson's disease) supported by Japan Science and Technology Corporation, Ministry of Education, Culture, Sports, Science and Technology of Japan

2001-Present Super Specialist (Senior Researcher)
Nutritional Neuroscience Physiology and Nutrition Group, Institute of Life Sciences Ajinomoto Co., Inc., Kawasaki, Japan

Technical Experiences

1971-1976
- Mechanism of brain damage and protective effect by feeding in neonatal mice with abuse dose of Glutamate.
- Genetical predisposition to hypertension and dietary salt intake in various strains of rats.

1977-1979
- Monell Chemical Senses Center: Biological mechanism of glutamate to taste receptor site of bovine tongue and synergistic enhancement by 5'-ribonucleotides.

1979-Present
- Central mechanism of preference change for amino acid with umami taste and sodium chloride in rats under various state of protein nutrition. (This is the main object for the Encouragement Award of Japanese Society of Nutrition and Food Science.)
- Appetite control and preference for nutrition in rats under various state of protein nutrition.

1990-1995
- Torii Nutrient-Stasis Project, ERATO, JRDC: Mechanism of homeostasis regulation by brain and development therapy for adult diseases with metabolic disorder.

Membership of Academic Societies

Japan se

Japanese Society of Nutrition and Food Science (Councilor)
Physiological Society of Japan
Japanese Neurochemical Society
Japanese medical Society of Alcohol Studies
Japanese Society for Comparative Endocrinology
Japan Society for Taste and Smell (Board Member)
Japan Society for the Study of Obesity (Councilor)
Japanese Society of Veterinary Science (Councilor)

Int rnational

Association for Chemoreception Sciences, USA
American Society for Neuroscience, USA
Society for the Study on Ingestive Behavior, USA
International Behavioral Neuroscience, USA (Board Member)
Nutritional Neuroscience, USA (Editor Board)

Selected List of Publications

Smriga, M. and Torii, K. (2003) 'Prolonged treatment with L-lysine and L-arginine reduces stress-induced anxiety in an elevated plus maze', *Nutritional Neuroscience*, vol.6, no.2, pp.125-128.

Smriga, M., Kameishi, M., Tanaka, T., Kondoh, T. and Torii, K. (2002) 'Preference for a solution of branched-chain amino acids plus glutamine and arginine correlates with free running activity in rats: involvement of serotonergic-dependent processes of lateral hypothalamus', *Nutritional Neuroscience*, vol.5, no.3, pp189-199.

Uneyama, H., Niijima, A., Tanaka, T. and Torii, K. (2002) 'Receptor subtype specific activation of the rat gastric vagal afferent fibers to serotonin', *Life Sciences*, vo.72, pp.415-423.

Kondoh, T., Uneyama, H., Nishino, H., and Torii, K. (2002) 'Melatonin reduces cerebral edema formation caused by transient forebrain ischemia in rats', *Life Sciences*, vol.72, pp.583-590.

Smriga, M., Kameishi, M., and Torii, K. (2002) 'Brief exposure to NaCl during early postnatal development enhances adult intake of sweet and salty compounds', *NeuroReport*, vol.13, no.18, pp.2565-9.

Smriga, M., Kameishi, M., Uneyama, H. and Torii, K. (2002) 'Dietary L-lysine deficiency increases stress-induced anxiety and fecal excretion in rats', *Journal of Nutrition*, vol.132, no.12, pp.3744-6.

Tabuchi, E., Yokawa, T., Mallick, H., Inubushi, T., Kondoh, T., Ono, T. and Torii, K. (2002) 'Spatio-temporal dynamics of brain activated regions during drinking behavior in rats', *Brain Research*, vol.951, no.4, pp.270-279.

Torii, K. and Niijima, A. (2001) 'Effects of lysine on afferent activity of the hepatic branch of the vagus nerve in normal and L-lysine-deficient rats', *Physiology and Behavior*, vol.72, no. 5, pp.685-90.

Tanimoto, H., Mori, M., Motoki, M., Torii, K., Kadowaki, M. and Noguchi, T. (2001) 'Natto mucilage containing Poly-γ-gulutamic acid increases soluble calcium in the rat small intestine', *Bioscience, Biotechnology, and Biochemistry*, vol.65, no. 3, pp.516-521.

Torii, K. and Niijima, A. (2001) 'Effect of lysine on afferent activity of the hepatic branch of the vagus nerve in normal and L-lysine deficient rats', *Physiology and Behavior*, vol.72, pp.685-690.

Tamura, R., Kondoh, T., Ono, T., Nishijo, H. and Torii, K. (2000) 'Altered activity of lateral and medial hypothalamic neurons in rats during discrimination of conditioned cue-tone stimuli in repeated cold stress', *Journal of Neurophysiology*, vol.84, no.6, pp.2844-58.

Smriga, M., Murakami, H., Mori, M. and Torii, K., (2000) 'Use of thermal photography to explore the age-dependent effect of monosodium glutamate, NACL and glucose on brown adipose tissue thermogenesis', *Physiology and Behavior*, vol.71, pp.403-407.

Smriga, M. and Torii, K., (2000) 'Release of hypothalamic norepinephrine during MSG intake in rats fed normal and nonprotein diet', *Physiology and Behavior*, vol.70, pp.413-415.

Smriga, M. and Torii, K. (2000) 'Preferable monosodium glutamate and sodium chloride solutions do not affect diurnal norepinephrine release in the rat lateral hypothalamus', *Nutritional Neuroscience*, vol.3, pp.367-372.

Smriga, M., Murakami, H., Mori, M. and Torii, K. (2000) 'Effects of L-lysine deficient diet on the hypothalamic interstitial norepinephrine and diet-induced thermogenesis in rats in vivo', *BioFactors*, vol.12, pp.137-142.

Smriga, M., Mori, M. and Torii, K. (2000) 'Circadian release of hypothalamic norephrine in rats in vivo is depressed during early L-lysine deficiency', *Journal of Nutrition*, vol.130, pp.1641-1643.

Fujimura, H., Ohsawa, K., Funaba, M., Murata, T., Takahashi, M., Abe, M. and Torii, K. (1999) 'Immunological localization and ontogenetic development of inhibin α subunit in rat brain', *Journal of Neuroendocrinology*, vol. 11.

Hawkins, R. L., Murata, T., Inoue, M., Mori, M. and Torii, K. (1998) 'Activin antiserum infused into the lateral hypothalamic area affects operant behavior of rats fed lysine-deficient diet', *Process of Society for Experimental Biology and Medicine*, vol.219, no.2, pp.149-153.

Tamura, R., Tanabe, K., Kawanishi, C., Torii, K. and Ono T. (1997) 'Effects of lentinan on abnormal ingestive behaviors induced by tumor necrosis factor', *Physiology & Behavior*, vol.61, no.3, pp.399-410.

Funaba, M., Murata, T., Murata, E., Ogawa, K., Abe, M., Takahashi, T. and Torii, K., (1997) 'Suppressed bone induction by Follistatin in Spontaneously Hypercholesterolemic Rat Bone', *Life Sciences*, vol.61, no.6, pp.653-658.

Murata, T., Takizawa, T., Funaba, M., Fujimura, H., Murata, E., Takahashi, M. and Torii, K. (1997) 'Quantitative RT-PCR for inhibin/Activin Subunits: measurement of rat hypothalamic and ovarian inhibin/ activin subunit mRNAs

during the estrous cycle', *Endocrine Journal*, vol.44, no.1, pp.35-42.

Murata, T., Takizawa, T., Funaba, M., Fujimura, H., Murata, E. and Torii, K. (1997) 'Quantitation of mouse and rat - actin mRNA by competitive polymerase chain reaction using capillary electrophorisis', *Analytical Biochemistry*, 244, pp.172-174.

Miura, Y., Murayama, H., Tsuzuki, S., Sugimoto, E. and Torii, K. (1997) 'Long-term consumption of an amino acid diet reduces the pancreatic enzyme secretion response to a trypsin inhibitor in rats', in 1997 ASNS Symposium Proceedings: *American Society for Nutritional Sciences Annual Meeting, April 6-9, 1997, New Orleans, Louisiana*, pp1377-1381.

Funaba, M., Murata, T., Fujimura, H., Murata, E., Abe, M. and Torii, K. (1997) 'Immunolocalization of type I or type II activin receptors in the rat brain', *Journal of Neuroendocrinology*, vol. 9, pp.105-111.

Funaba, M., Murata, T., Fujimura, H., Murata, E., Abe, M., Takahashi, M. and Torii, K., (1996) 'Unique recognition of activin and inhibin by polyclonal antibodies to inhibin subunits', *The Journal of Biochemistry*, vol.119, pp.953-960.

Torii, K., Yokawa, T., Tabuchi, E., Hawkins, R. L., Mori, M., Kondoh, T. and Ono, T. (1996)'Recognition of deficient nutrient intake in the brain of rat with L-lysine deficiency monitored by functional magnetic resonance imaging electrophysiologically and behaviorally, *Amino Acids*, 10, pp.73-81.

Murata, T., Saito, S., Shiozaki, M., Lu, R. Z., Eto, Y., Funaba, M., Takahashi, M. and Torii, K. (1996) 'Anti-activin A antibody(lgY) specifically neutralizes various activin A activities', *Process of Society for Experimental Biology and Medicine*, vol.211, no.1, pp100-107.

Tabuchi, E., Uwano, T., Kondoh, T., Ono, T. and Torii, K. (1996) 'Contribution of chorda tympani and glossopharyngeal nerves to taste preferences of rat for amino acids and NaCl', *Brain Research*, 739, pp.139-155.

Yokawa, T., Tabuchi, E., Takezawa, M., Ono, T. and Torii, K. (1995) 'Recognition and Neural Plasticity Responding to Deficient Nutrient Intake Scanned by a Functional MRI in the Brain of Rats with L-Lysine Deficiency', *Obesity Research*, vol.3 Supplement, pp.685S - 688S.

Hawkins, R. L., Inoue, M., Mori, M., and Torii, K. (1995) 'Effect of inhibin, follistatin, or activin infusion into the lateral hypothalamus on operant behavior of rats fed lysine deficient diet', *Brain Research*, vol.704, pp.1-9.

Inoue, M., Funaba, M., Hawkins, R. L., Mori, M. and Torii, K. (1995) 'Effect of continuous infusion of lysine via different routes and hepatic vagotomy on dietary choice in rats', *Physiology and Behavior*, vol.58, no.2, pp.379-385.

Hawkins, R. L., Inoue, M., Mori, M. and Torii, K. (1994) 'Lysine deficient diet and lysine replacement affect food directed', Physiology and Behavior, vol. 56, no. 5, pp.1061-1068.

Tabuchi, E., Kondoh, T., Voynikov, T., Yokawa, T., Ono, T. and Torii, K. (1994)'Lateral hypothalamic neuron response to application of amino acids in different nutritive conditions olfaction and taste', in Kurihara, K., Suzuki, N., and Ogawa, H. (eds) *Operant Behavior XI*, Tokyo: Springer-Verlag.

Torii, K., Hanai, K., Oosawa, K., Funaba, M., Okiyama, A., Mori, M., Murata, T. And Takahashi, M. (1993) 'Activin A: serum levels and immunohistochemical brain localization in rats give diets deficient in L-lysine or protein', *Physiology and Behavior*, vol. 54, pp.459-466.

Mori, M., Kawada, T. and Torii, K. (1991) 'Appetite and taste preference in growing rats given various levels of protein nutrition', *Brain Research Bulletin*, vol. 27, pp.417-422.

Mori, M., Kawada, T., Ono, T. and Torii, K., 'Taste preference and protein nutrition and L-Amino Acid homeostasis in Male Sprague-Dawley Rats', *Physiology & Behavior*, vol.49, pp.987-995.

Torii, K., Kawada, T. and Masato Mori, M. (1990) 'Appetite and taste preference for amino acids and sodium chloride in growing rats with protein nutrition', in Oomura, Y., Tarui, S., Inoue, S. and Shimazu, T. (eds) *Progress in Obesity Research*, London: John Libbey & Company Ltd., chapter 8, pp.41-46.

Torii, K., Mimura, T. and Yugari, Y. (1986) 'Effects of dietary protein on the taste preference for amino acids in rats', in Kare, M. K. and Brand, J. G. (eds) *Interaction of the Chemical Senses with Nutrition*, Orlando: Academic Press, Inc.